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GRUMBLING, M

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ART UNIT

PAPER NUMBER

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1202
DATE MAILED:

10/13/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on _____ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 1 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice re Patent Drawing, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, Form PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6. _____

Part II SUMMARY OF ACTION

1. Claims 1-25 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. Claims 4-16 have been cancelled.

3. Claims _____ are allowed.

4. Claims 1-3, 17-25 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable. not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been approved by the examiner. disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed on _____, has been approved. disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

Serial Number: 08/278,112

-2-

Art Unit: 1202

This is a file wrapper continuation of Serial Number 07/578,942. Claims 1-3 and 17-25 are pending.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-3 and 17-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Brattsand et al. '233.

The '233 reference generically teaches compounds of formula (I) in columns 1-2, lines 20-35 which are taught to be useful *inter alia* as anti-inflammatory agents. The claims differ from

Serial Number: 08/278,112

-3-

Art Unit: 1202

the reference in reciting a more narrow genus and different species than those of the '233 reference. However, one of ordinary skill in the art would have been motivated to select any of the compounds embraced by the '233 reference, including those of the instant claims, because they are taught to be equivalent and therefore are presumed to be so similar in structure and function as to have very similar properties. The instant claims would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2-3 and 22-23 are limited to the R- or S- epimer of the generically or specifically claimed compounds. Although Brattsand et al. do not specifically teach these optical isomers of their compounds, one of ordinary skill in the art would have been motivated to isolate one or the other optical isomer because it is well known in the pharmaceutical art that all or most of a compound's biological activity resides in one optical isomer. *In re Adamson et al.* (CCPA 1960) 275 F2d 952, 125 USPQ 233. *Brenner et al. v. Ladd. Comr. Pats.* (DCDC 1965) 247 FSupp 51, 147 USPQ 87. One of ordinary skill in the art would therefore have been motivated to prepare optical isomers of the compounds taught by Brattsand et al. '233 at the time the instant invention was made because one of ordinary skill in the art would have expected such purified optical isomers to have similar if not superior properties as compared to those of the racemate.

Art Unit: 1202

Claims 2-3 and 22-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Brattsand et al. '233 in view of Brattsand et al. '534. The primary reference, '233, teaches compounds of formula (I) in columns 1-2, lines 20-35 which are taught to be useful *inter alia* as anti-inflammatory agents. The claims differ from the primary reference as described above and also in that they are limited to particular optical isomers of the generically claimed compounds of claim 1. The secondary reference, '534, teaches that it is desirable to isolate particular optical isomers because they have superior properties over the racemates. Thus, one of ordinary skill in the art would have selected the particular optical isomers of the instant claims at the time the invention was made because they would have been expected to have at least similar if not superior properties over those of Brattsand '233.

In order to attempt to overcome the above rejections, applicants have filed a declaration (on 6/25/93). The declaration has been fully considered and the above rejections of the claims have been reconsidered in light thereof. For reasons set forth below, the above rejections are maintained.

In the declaration, declarant Conde sets forth several separate pieces of evidence to support his conclusion that the instant claims are not obvious in view of the Brattsand et al. references. Each of these pieces of evidence have been

Art Unit: 1202

considered separately and together but none are persuasive either separately or in combination with the other evidence.

1) Declarant argues that the homologous series of examples 1, 2 and 3 are so different as to negate any presumption of obviousness based upon homology in the instant case. The examiner rejects this line of reasoning. Examples 1, 2 and 3 are not the closest prior art of record (examples 16, 22 and 24 have been previously identified as such) and any comparison must be based upon the closest prior art of record. Even if one were to accept the tests as valid, the conclusion drawn therefrom is incorrect. Homologs are well known in the art to differ from each other in properties, however it is also well known that such differences vary gradually over a homologous series, and therefore one of skill in the art would be motivated to prepare one member of the series with the expectation that it would have similar properties. *In re Hass et al.* (CCPA 1944) 141 F2d 122, 60 USPQ 544, *In re Henze* (CCPA 1950) 181 F2d 196, 85 USPQ 261. The results summarized in the table on page 5 of the declaration do nothing more than establish what range of values are to be expected within an homologous series within the scope of the Brattsand et al. '233 patent disclosure. Clearly a relatively wide range of values (a factor of at least ten in therapeutic index) is to be expected. This does not contradict, rather it affirms, the presumptions of the Hass-Henze doctrine.

Art Unit: 1202

The compounds of examples 1-3 do have similar properties, although they differ in degree. What declarant has established it that in order for declarant to overcome the presumption of obviousness under the Hass-Henze doctrine, he must establish much more than a ten fold difference in degree between the claimed compounds and those of the prior art.

On page 6 of the declaration, declarant compares example 16 of Brattsand '233 and EL-854. It is impossible for the examiner to evaluate this comparison since EL-854 is not identified. It isn't even clear that EL-854 is a compound within the scope of the instant invention, merely that its pharmacological activity is recorded in proprietary files. Moreover, the difference in ED₅₀ values of factors of 3 and 5 respectively are not seen to be significant since a homologous series, i.e. very closely related compounds, differ by a factor of ten or more.

On page 8 comparison is made with compounds of McDonald. These comparisons are irrelevant because McDonald is not the closest prior art of record. Moreover, of the compounds identified as 7, 10 and 13 of the instant specification only 10 is relevant since 7 and 13 both bear a cyclohexane ring at the R² position. None of the Brattsand et al. compounds possess such a substituent at this position. Comparing the values of example 22 of Brattsand '233 and compound 10 of the instant invention, the differences are so slight as to be of questionable statistical

Serial Number: 08/278,112

-7-

Art Unit: 1202

significance. This is especially true since it is not clear that the prior art compound and the compound of the instant invention were tested under identical conditions. It is possible that the Brattsand et al. compound could have been of lesser purity, or that the prior art tests could have been done under less favorable conditions than those of the instant invention. Since it is not clear how the compounds were tested, and since the differences really are not that great (1.49 versus 2.73) the data are not convincing of unobviousness.

Again the results compared on page 11 of the declaration are not convincing of unobviousness. Declarant has chosen to compare examples 1, 3, 7, 8 and 12 of the Brattsand '534 reference with compounds of the instant invention. This is not convincing because the closest prior art compounds have not been tested against the closest compounds of the instant invention. It is stressed that Brattsand '534 was and is relied upon only to teach the notion that it is known to isolate and use one optical isomer of a racemic mixture of steroids because it will have similar if not superior properties over the racemate. The declaration does nothing to overcome this presumption.

For the above reasons, the examiner maintains the above rejections under 35 U.S.C. § 103.

NEW GROUNDS OF REJECTION

Art Unit: 1202

Applicants have made available publications previously unavailable to the examiner which necessitate the new grounds of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 17-21 and 24-25 are rejected under 35 U.S.C.

§ 102(a) or (b) as being anticipated by WHO DRUG INFORMATION 3(4) (WHO). The claims read on 11 β ,16 α ,17,21-tetrahydroxypregna-1,4-3,20-dione, cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate (126544-47-6) on page 210, third compound.

Claims 1, 17-20, and 24-25 are rejected under 35 U.S.C.

§ 102(b) as being anticipated by Acta Pharmaceutica Suecica vol 19, no. 5 (APS-19). The claims read on number XIV, i.e. the compound wherein Y = X = H, R₁ = H, R₂ = CH(CH₃)₂, R₃ = COCH₃Me and R₄ = H (see the formula at top of page 329).

Claims 1, 17-20, and 24-25 are rejected under 35 U.S.C.

§ 102(b) as being anticipated by Acta Pharmaceutica Suecica vol 21, no. 2 (APS-21). The claims read on number 35, i.e. the

Serial Number: 08/278,112

-9-

Art Unit: 1202

compound wherein Y = X = H, R₁ = CH(CH₃)₂, R₃ = Me and R₄ = H (see the formula at top of page 113).

Claims 1-3 and 17-25 are rejected under 35 U.S.C. § 103 as being unpatentable over WHO, APS-19, or APS-21. The references independently teach glucocorticosteroid compounds which have anti-inflammatory activity. The instant claims are drawn to structurally similar compounds which differ only in that they are drawn to the corresponding optical isomers. One of ordinary skill in the art would have been motivated to isolate one or the other optical isomer because it is well known in the pharmaceutical art that all or most of a compound's biological activity resides in one optical isomer. *In re Adamson et al.* (CCPA 1960) 275 F2d 952, 125 USPQ 233. *Brenner et al. v. Ladd. Comr. Pats.* (DCDC 1965) 247 FSupp 51, 147 USPQ 87. One of ordinary skill in the art would therefore have been motivated to prepare optical isomers of the compounds taught by the references at the time the instant invention was made because one of ordinary skill in the art would have expected such purified optical isomers to have similar if not superior properties as compared to those of the racemate.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Serial Number: 08/278,112

-10-

Art Unit: 1202

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew V. Grumbling whose telephone number is (703) 308-4713. The examiner can usually be reached on Monday through Friday from 9:30 a.m until 6:00 p.m.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

A facsimile center has been established in Group 1200, room 3C10. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine are (703) 308-4556 or 305-3592.

Matthew V. Grumble
Matthew V. Grumbling
Patent Examiner
GAU 1202
October 4, 1994